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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 29

Serial Number: 08/823,999

Filing Date: 3/25/97

Appellant(s): Rogers et al.

Patrea L. Pabst
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's Brief on appeal filed 6/22/00 (Paper No. 22).

The text of those sections of Title 35 U.S.Code not included in this appeal can be found in a previous Office action herein.

(1) Real Party of Interest.

A statement identifying the real party of interest is contained in the Brief.

(2) Related Appeals and Interferences Identified.

A statement identifying that no related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the Brief.

(3) Status of Claims.

The statement of the status of claims contained in the Brief is correct.

This appeal involves claims 1-6, 8 and 10-12 as the claims read on Mac-1, as the elected invention. It is noted that ICAM-1 is the ligand for Mac-1.

The claims set forth in Appendix II: Claims as proposed to be amended are under appeal.

(4) Status of Amendments After Final.

Appellant's statement of the status of amendments after final rejection contained in the Brief is correct.

Appellant's amendment, filed 6/22/00 (Paper No. 21), with the Appeal Brief (Paper No. 22), is acknowledged and has been entered.

Claims 1, 5, 6 and 8-10 have been amended.

The claims set forth in Appendix II: Claims as proposed to be amended are under appeal.

(5) Summary of Invention.

The summary of invention contained in the Brief is essentially correct.

It is noted that the claims are drawn to a method of inhibiting or reducing stenosis or restenosis of a blood vessel following injury to vascular tissue in a region of a blood vessel comprising administering a compound which specifically inhibits or reduces leukocyte integrin mediated adhesion or function, where the integrin is selected from the group consisting of Mac-1 (CD11b/CD18), LFA-1 (CD11a/CD18), p150,95 (CD11c/CD18) and CD11d/CD18), wherein the compound is an antibody, antibody fragment, molecule, peptide or peptidomimetic which binds, inhibits or blocks the expression or function of the integrin or its ligand.

It is noted that coronary angioplasty is now a widely used and effective method of revascularization for many patients with atherosclerotic coronary artery disease. The following two problems remain. The first is the short-term problem of ischemic complications due to reocclusion or abrupt reclosure of the treated artery, within a day or so after an angioplasty procedure. The second is the longer-term problem of recurrence or restenosis of the underlying atherosclerotic lesion; which typically manifests itself within 3-6 months after treatment.

In addition, it is noted that stenosis refers to a narrowing or stricture of a duct or canal and in vascular bypass surgery refers to occluded blood vessels.

(6) Issues.

Appellant's statement of the issues in the Brief is incorrect.

Claims 1-6, 8 and 10 are rejected under 35 U.S.C. § 102(b) by Simon et al. (Circulation 92, 8 Supp: 1-110, Abstract 0519, 1995) and not under 35 U.S.C. § 102(e).

The indication of a 102(e) rejection with respect to Simon et al. (Circulation, 1995) in the previous Office Actions (Paper Nos. 10 and 14) was clearly a typographical error.

Simon et al. is not a U.S. Patent and is not available as art under 35 U.S.C. § 102(e).

Further, it is noted that the 35 U.S.C. § 102(b) statute was indicated on page 4, Section 8 of Paper No. 10 in the first Office Action on the merits.

In contrast to appellant's statement that the claims are held obvious in view Ricevuti et al. AND/OR, Albelda et al. AND/OR Coller et al. AND/OR Simon et al. in view of "unidentified art for administering pharmaceutical compositions" and Neumann et al.;

the rejection under 35 U.S.C. § 103 stated "in view of art known use of administering pharmaceutical reagents in various composition forms and at various intervention times".

Therefore, the rejection has taken official notice that the use of administering pharmaceutical reagents in various composition forms and at various intervention times was well known and practiced by the ordinary artisan at the time the invention was made in meeting the needs of the patient.

Appellant has not seasonably challenged these well known statements of record. See MPEP 2144.03.

It is noted that the rejection under 35 U.S.C. 112, first paragraph, has been drawn to the instant methods as they read on inhibiting or reducing stenosis or restenosis of a blood vessel following injury to vascular tissue with a myriad of structurally distinct compounds (e.g. molecule, peptides, peptidomimetics) to a variety of diverse targets (e.g. CD11a/CD18, CD11b/CD18, CD11c/CD18, CD11d/CD18 integrins and their ligands).

It is noted that the art rejections under 35 U.S.C. § 102 and 35 U.S.C. § 103 have been drawn to the instant methods as they read on the elected invention of antibodies that bind Mac-1.

(7) Grouping of Claims.

Appellant's Brief includes a statement that claims do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

It is acknowledged the claims are drawn to different subject matter, which raise different issues under 35 U.S.C. 112, first paragraph, as well as 35 U.S.C. § 102 and 35 U.S.C. § 103

Again; the claims are read in the context of the anti-Mac-1 antibodies as the elected compound of the claimed invention; the rejection under 35 U.S.C. 112, first paragraph address the breadth of the claimed methods relying upon "any compound which specifically inhibits or reduces leukocyte-integrin-mediated expression or interaction".

Further, it is noted the appellant's statement in the Brief that certain claims do not stand or fall together is not agreed with because it states that claims 3 and 11 contain limitations not disclosed at all by the prior art. However, appellant has not appeared to have seasonably traversed this aspect of the prior art rejections, nor has addressed this aspect of the prior art rejections in this Brief.

(8) Claims Appealed.

The copy of the appealed claims contained in Appendix II Claims as proposed to be amended attached to the Brief is correct.

As pointed out above; appellant's amendment, filed 6/22/00 (Paper No. 21), with the Appeal Brief (Paper No. 22), is acknowledged and has been entered

(9) Art of Record.

The following is a listing of the art of record relied upon in the rejection of claims under appeal.

- ✓ A) Albelda et al.; FASEB J 8: 504-512 (1994).
- ➔ B) Edgington; Biotechnology 20: 383-389 (1992).
- C) Coller et al.; U.S. Patent No. 5,770,198.
- ✓ D) Genetta et al.; Annals of Pharmacology 30: 251-257 (1996).
- ✦ E) Neumann et al.; J Am Col Cardiol 27: 819-824 (1996).
- ✓ F) Ricevuti et al.; Atherosclerosis 91: 1-14 (1991).
- ✦ G) Simon et al.; Circulation 92 (8 Suppl): I-110, Abstract 0519 (1995).
- ✦ H) Simon et al.; Arterioscler Thromb Vasc Biol: 17: 528 - 535 (1997).

The following is a listing of art relied upon by appellant as Exhibits in addressing the rejections of record.

- ✓ I) Coats et al.; Semin Interv Cardiol 2: 153 - 158, 1997; Exhibit.
- ✓ J) Deitch et al.; Arterioscler Thromb Vasc Biol 18: 1730-1737, 1998; Exhibit.
- ✓ K) The Eraser Investigators; Circulation 100: 799-806, 1999; Exhibit.
- ✓ L) Farb et al.; Circulation 99: 44-52, 1999; Exhibit.
- ✓ M) Folts et al.; J Am Coll Cardiol 33: 295-303, 1999; Exhibit.
- ✓ N) Kearney et al.; Circulation 95: 1998-2002, 1997; Exhibit.
- ✓ O) Komatsu et al.; Circulation 98: 224-233, 1998; Exhibit.
- ✓ P) Mikelson et al.; J Am Coll Cardiol 33: 97-106, 1999; Exhibit.
- ✓ Q) Simon et al.; J Clin Invest 105: 293-300, 2000; Exhibit.
- ✓ R) Topol et al.; JAMA 278: 479-484, 1997 Exhibit.

(10) Grounds of Rejection.

The following ground(s) of rejection are applicable to the appealed claims.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-6, 8, 11 and 12 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs such as antibodies can be species- and model-dependent, it is not clear that reliance on the in vitro and in vivo evidence of inhibiting leukocyte-integrin-mediated adhesion with Mac-1-specific antibodies accurately reflects the relative efficacy of the claimed methods relying upon any "compound which specifically inhibits or reduces leukocyte-integrin-mediated adhesion or function" (e.g. compounds, molecules, peptides, peptidomimetics).

Although the claims are read in the context of the anti-Mac-1 antibodies as the elected compound of the claimed invention; the following is noted as the claims read on "a compound which specifically inhibits or reduces leukocyte-integrin-mediated adhesion.

The instant claims encompass and are broadly drawn to "compounds" which encompass any compound, integrin, ligand, molecule, peptide or peptidomimetics capable of inhibiting or reducing leukocyte-integrin-mediated adhesion. However, the claims do not recite sufficient structural elements or specificity for the compounds encompassed by the claimed methods. The specification does not provide sufficient guidance and direction to identify and to enable any compound which might inhibit or reduce leukocyte-integrin-mediated adhesion.

Additionally, all the claimed methods encompass in vivo administration of compounds, and as it has been well known to the skilled artisan that dosage parameters and administration protocols vary from molecule to molecule depending on clearance and reactivity of the molecule with internal factors. Therefore, in view of the breadth of the claims and the unpredictability in the art, and in view of the insufficient guidance and working examples in the specification, the quantity of experimentation required by one skilled in the art to practice the invention undue.

The following is noted with respect to inhibiting integrin-mediated inhibition.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In addressing adhesion-based therapy, Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (Edgington, Biotechnology, 1992; see entire document, particularly page 386, column 3, paragraph 4). The inherent difficulties of this approach include development of serum sickness after injection of foreign protein, diminishing therapeutic effects after prolonged therapy and the potential for promotion of infection.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective adhesion-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive for the breadth of compounds which specifically inhibits or reduces leukocyte-integrin-mediated adhesion.

Rejection Under 35 U.S.C. § 102(b)

As pointed out above in Section 6; the previous indication of a 102(e) rejection with respect to Simon et al. (Circulation, 1995) in the previous Office Actions (Paper Nos. 10 and 14) was clearly a typographical error.

Claims 1-6, 8 and 10 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Simon et al. (Circulation 92, 8 Suppl: I-110, Abstract 0519, 1995). Simon et al. teach that the 7E3 antibody is used to inhibit ischemic complications of coronary angioplasty and clinical restenosis and that this 7E3 antibody cross-reacts with Mac-1 (see Abstract).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods using 7E3 antibodies.

Rejection Under 35 U.S.C. § 102(e)

Claims 1-6, 8 and 10-12 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Coller et al. (U.S. Patent No. 5,770,198), as further evidenced by Simon et al. (Circulation 92, 8 Suppl: I-110, Abstract 0519 (1995). Circulation, 1995). Coller et al. teach the use of the 7E3 antibody to treat a number of thrombotic conditions (see entire document, including Utility of Platelet-Specific Chimeric immunoglobulin in columns 5-7). Simon et al. provides evidence that the 7E3 antibody cross-reacts with Mac-1 (see entire document).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods using 7E3 antibodies.

Rejection Under 35 U.S.C. § 103

Claims 1-6, 8, 10-12 stand rejected under 35 U.S.C. § 103 as being unpatentable over Ricevuti et al. (Atherosclerosis 91: 1-14, 1991) AND/OR Albelda et al. (FASEB J. 8: 504-512, 1994) AND/OR Coller et al. (U.S. Patent No. 5,770,198) AND/OR Simon et al. (Circulation 92, 8 Suppl: I-110, Abstract 0519, 1995) in view of art known use of administering pharmaceutical reagents in various composition forms and at various intervention times and in further evidence of Neumann et al. (JACC 27: 819-824, 1996).

Ricevuti et al. teach inhibiting PMNs via anti-CD11b/CD18 antibodies to inhibit ischemia-reperfusion injury (see entire document, including the Abstract). This reference differs from the instant methods by not disclosing Mac-1-specific antibodies to inhibit restenosis and stenosis per se.

Albelda et al. teach the use of adhesion molecule-specific including blockade of the CD11/CD18 complex has been show to inhibit neutrophil influx in almost every system to date including the heart and ischemia reperfusion (see entire document, including page 508, column 2, CD11/CD18).

Ricevuti et al. and Albelda et al. differ from the instant methods by not disclosing the use of Mac-1-specific antibodies to inhibit stenosis and restenosis per se, however such therapeutic methods would have readily discerned by the teaching indicated of inhibiting neutrophil influx and inflammation in ischemia-reperfusion injury.

Coller et al. teach the use of the 7E3 antibody to treat a number of thrombotic conditions (see entire document, including Utility of Platelet-Specific Chimeric immunoglobulin in columns 5-7).

Simon et al. teach that the 7E3 antibody is used to inhibit ischemic complications of coronary angioplasty and clinical restenosis and that this 7E3 antibody cross-reacts with Mac-1 (see Abstract).

Given the additional teachings of Collier et al. and Simon et al., the ordinary artisan would have had motivation and an expectation of success that the use of anti-Mac-1 specific antibodies would inhibit stenosis and restenosis associated with vascular intervention given that a property of the 7E3 antibody was to bind and inhibit via the Mac-1 specificity.

As further evidence that the Mac-1 specificity was an important target in treating complications associated with vascular intervention, Neumann et al. teaches the art known role of neutrophil and platelet activation, including the Mac-1 specificity (see entire document).

The ordinary artisan would have applied different formulations and times of administration known and practiced at the time the invention was made to inhibit complications associated with vasculature intervention. The claimed formulations and times of administration were either taught by the references above or obvious to the ordinary artisan in treating different patients and different complications associated with different procedures.

One of ordinary skill in the art at the time the invention was made would have been motivated to select Mac-1 specific antibodies to inhibit restenosis and stenosis as a therapeutic regimen in treating complications associated with vascular interventions. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(11) Response to Argument

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-6, 8, 11 and 12 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention as the claims read on "a compound which specifically inhibits or reduces leukocyte-integrin-mediated adhesion or function" for the reasons of record.

Appellant's arguments, in conjunction with legal citations and Exhibits, have been fully considered but are not found convincing essentially for the reasons of record and addressed herein.

It is noted that appellant acknowledges that despite cell culture and small animal data supporting the regulatory role of heparin-like compounds, exogenous heparin preparations have shown no benefit in human trials (see page 8, lines 4-6 of the Brief).

It is noted that appellant acknowledges that one skilled in the art would not expect a single compound to be effective in limiting or preventing restenosis (see pages 8-9, overlapping paragraph of the Brief).

It is noted that in response to the rejections under 35 U.S.C. § 102; appellant states that treatment of thrombotic complications (i.e. ischemia and ischemia-reperfusion injury) is not the same as, nor predictive of the treatment of patients to prevent or reduce restenosis (see page 17 paragraph 1 of Section C of the Brief).

In contrast to this lack of predictability based upon cell culture and small animal data in treating restenosis; appellant asserts that the results obtained by appellant showing that a single class of compounds, compounds blocking binding and activation of certain integrins could effectively limit restenosis, were completely unexpected.

However, it is noted that appellant has relied upon observations of the inhibition of a single compound (the anti-Mac-1 M1/70 antibody) in in vitro binding assays (Example 1) and in an experimental rabbit model (Example 2) (see pages 22-23 of the specification). Also, it is noted that the M1/70 was administered two hours prior to surgical intervention and for two weeks after arterial injury. The rabbits were sacrificed after two weeks and arteries were examined; a time period that does not necessarily reflect restenosis, which is a longer term problem usually occurring three to six months after treatment.

There is insufficient objective evidence that a single compound such as the M1/70 antibody in experimental models, as disclosed in the specification as filed, can be extrapolated to predict the efficacy of a myriad of diverse "compounds that inhibit or reduce CD11/CD18 adhesion or function" (e.g. molecules, peptides, peptidomimetics) in the claimed methods to inhibit or reduce stenosis or restenosis, commensurate in scope with the claimed invention.

In contrast to appellant's assertions; the claims are not limited to the use of a single class of compounds but rather encompass a broad range of distinct compounds and specificities. The claimed methods encompass targeting a variety of integrin members (e.g. CD11a/CD18; CD11b/CD18; CD11c/CD18; CD11d/CD18) (or their ligands) and administering a variety of structurally diverse compounds (e.g. antibodies, molecules, peptides, peptidomimetics, antisense oligonucleotides, ribozymes).

There is insufficient objective evidence that the skilled artisan would predict that such a diverse class of compounds specific for various targets would be recognized as a single class of compounds to reduce or inhibit stenosis or restenosis of a blood vessel following injury to vascular tissue.

Appellants' disclosure of the definition and of the methods of screening for these compounds as well as the modes of their administration is acknowledged.

However, in view of the lack of predictability of the art to which the invention pertains (reducing or inhibiting restenosis), as acknowledged by the skilled artisan as well as by appellant's admissions; methods of treating restenosis with a broad range of structurally diverse compounds to a variety of diverse specificities would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

Appellant asserts on page 13, last sentence of the Brief that the examiner has not responded to certain evidence; however the evidence provided by appellant was considered previously and not considered convincing to overcome the rejection under 35 U.S.C. 112, first paragraph.

Appellant relies upon Simon et al. (Circulation 100, 18 Suppl I: page I-332, Abstract 1742, 1999; Exhibit) to support that assertion that an equivalent effect can be obtained with a peptide inhibitor.

However, Simon et al. discloses the identification and characterization of the M25 peptide as the first extracellular domain sequence of an integrin which broadly impairs integrin adhesion and migration to matrix proteins without directly inhibiting ligand binding.

The M25 peptide disclosed in this Simon et al. reference was not disclosed or contemplated by the specification as filed and appears to possess properties distinguishable from the claimed and disclosed compounds as filed to be used in the claimed methods (see Abstract).

It is not clear that the M25 peptide has an equivalent effect as the instantly disclosed M1/70 antibody or the prior art 7E3 antibody; as the M25 was tested in vitro and not in an in vivo setting (see Abstract).

Appellant asserts on page 13, last sentence of the Brief that the examiner has not responded to this evidence; however this evidence was considered previously and did not provide sufficient objective evidence to support the breadth of diverse compounds to be used in the claimed methods.

As pointed out previously; in addressing adhesion-based therapy, Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (Edgington, Biotechnology, 1992; see entire document, particularly page 386, column 3, paragraph 4).

As pointed out above, appellant acknowledges the art known difficulties in treating restenosis and the reliance upon in vitro and in vivo experimental models; yet relies upon in vitro and in vivo observations employing a single disclosed anti-Mac-1 antibody in experimental models to be predictive of a broad range of diverse compounds, which are structurally distinct and operate via distinct modes of action.

In contrast to appellant's assertions; appellant is not required to provide in vivo data to demonstrate that a therapy will be effective, but rather is requested to provide objective evidence that would be predictive of the claimed invention of methods to inhibit or reduce stenosis or restenosis.

The scope of the required enablement varies inversely with the degree of predictability involved and in cases involving unpredictable factors such as physiological activity more may be required. See MPEP 2164.03 and 2164.02.

Given the relatively incomplete understanding in the biotechnological field involved and the lack of a reasonable correlation between the narrow disclosure in the specification and broad scope of protection sought in the claims; the lack of enablement is deemed appropriate. See MPEP 2164.08.

Appellant argues that Coats et al. (Semin. Interv. Cardiol. 2: 153 - 158, 1997; Exhibit) notes that animal studies in remodeling and its contribution to restenosis have been critical and correlated with human studies.

It is acknowledged that both in vitro and in vivo experimental models validate concepts associated with or based upon human disease.

However, the issue at hand is the predictability of inhibiting stenosis and restenosis with the scope of CD11/CD18 antagonists encompassed by the claimed methods; given the limited disclosure by appellant and the art recognized difficulty in treating restenosis.

Appellant argues that Farb et al. (Circulation 99: 44-52, 1999; Exhibit) discloses that data in the pig model regarding inflammation and thrombus closely reflect the findings observed in human coronary stenting.

Appellant also acknowledges that there is a difference in the type of vascular injury in normal arteries of animals as compared to the response in human atherosclerotic arteries (see page 51, column 2).

Here, Farb et al. states that the type of vascular injury in stented normal arteries in experimental animals differs considerably from that in human atherosclerotic arteries (see page 51, column 2).

Farb et al. is drawn to observations associated with descriptive pathology and does not provide objective evidence to support the breadth of CD11/CD18 antagonists in the treatment of restenosis.

Appellant argues that Komatsu et al. (Circulation 98: 224-233, 1998; Exhibit) reports that animal models are generally predictive, with dogs as the exception.

Komatsu et al. states that despite similarities between experimental animal models and humans, the study also show important differences in the healing phenomena after stenting (see page 230, column 1, paragraph 1).

It is noted that Komatsu et al. indicates that the study is limited by the number of cases (see page 232, column 2; Study Limitations)

Also, Komatsu et al. is drawn to observations associated with descriptive pathology and does not provide objective evidence to support the breadth of CD11/CD18 antagonists in the treatment of restenosis.

Further, Komatsu et al. states that coronary stenting is the only procedure that has been proven to reduce the incidence of late restenosis after PCTA (see page 224, column 1, first sentence).

Appellant asserts that Kearney et al. (Circulation 95: 1998-2002, 1997; Exhibit) correlates results in humans obtained at autopsy with animal studies; however this asserted correlation is not readily apparent.

Kearney et al. does state that although animals models have failed to disclose evidence of site-specific variation in the histopathology of in-stent neointimal thickening, it must be acknowledged that the extent to which the pathological features of in-stent restenosis described in lower-extremity vasculatory can be extrapolated to other vascular beds, as well as other types of stents, awaits further confirmation.

Kearney et al. is drawn to observations associated with descriptive pathology and does not provide objective evidence to support the breadth of CD11/CD18 antagonists in the treatment of restenosis.

Appellant argues that Folts et al. (J. Am. Coll. Cardiol. 33: 295-303, 1999; Exhibit) notes that the animal model with the cyclic flow model of coronary thrombosis has been useful in predicting which agents are likely to be of benefit clinical trials.

It is acknowledged that cyclic flow models are useful screening for platelet inhibitors; however the claims encompass methods of inhibiting restenosis.

Folts et al. discloses that conditions such as unstable angina, angioplasty, coronary stenting and thrombolysis are likely to require more potent platelet inhibitors (see page 301, column 1; Summary).

Appellant argues that Simon et al. (J. Clin. Invest. 105: 293-300, 2000; Exhibit) describes the role of inflammation in mechanical arterial injury.

However as appellant acknowledges; this is limited to Mac-1 and its total absence in an experimental mouse model rather than targeting a variety of integrin (or ligand) targets with diverse compounds in order to inhibit stenosis or restenosis.

Appellant appears to cite that Topol et al. (JAMA 278: 479-484, 1997; Exhibit) in supporting pharmaceutical compositions in the treatment of ischemic events.

It is noted that this study by the EPIC Investigator Group reads on the elected invention, which is considered enabled, and also is met by the prior art teachings of record and herein.

Here, Topol et al. states that a large number of pharmacological agents have failed to reduce restenosis or improve long-term clinical outcomes and that only the large-scale trial that reported an effect was using abciximab (see page 479, right hand column).

Again, it is noted that the referenced abciximab is a monoclonal antibody fragment against $\alpha IIb\beta 3$, which cross-reacts with Mac-1 and is derived from the 7E3 antibody of the prior art rejections.

This reference clearly supports the rejections under 35 U.S.C. 112, first paragraph, as well as under 35 U.S.C. 102 and 103 of record and reiterated herein.

In contrast to appellant's assertions that there is insufficient support for alleging that the application is non-enabling and that there has been a lack of rebuttal by the examiner; the record is replete with statements and evidence as well as appellant's admissions that treating restenosis has been highly unpredictable in the art, including at the time the invention was made; and that relying upon a limited number of working examples in experimental models (e.g. M1/80 antibody in Examples 1 and 2 in the specification as filed) would not be predictive of the ability of a large genus of diverse pharmacological agents to reduce stenosis restenosis in vivo in a clinical setting, as encompassed by the claimed methods and as asserted by appellant's arguments.

Appellant's arguments are not found persuasive.

Rejection Under 35 U.S.C. § 102(b) and § 102(e)

Claims 1-6, 8 and 10 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Simon et al. (Circulation, 1995).

Claims 1-6, 8 and 10-12 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Coller et al. (U.S. Patent No. 5,770,198), as further evidenced by Simon et al. (Circulation, 1995).

Appellants arguments have been fully considered but are not found convincing for the reasons of record and addressed herein.

Appellant states that treatment of thrombotic complications (i.e. ischemia and ischemia-reperfusion injury) is not the same as, nor predictive of, treatment of patients to prevent or reduce restenosis.

Appellant argues that Mikelson et al. (J. Am. Coll. Cardiol. 33: 97-106, 1999; Exhibit) show that the 7E3 antibody Fab (ReoPro) decreases detectable CD11b on neutrophils but does not bind to neutrophils nor inhibit adhesion; two of the major factors involved in restenosis.

While Mikelson et al. disclose that the expression of CD11b on "isolated" monocytes was not changed by the incubations with chimeric 7E3 Fab; Mikelson et al. disclose that chimeric 7E3 Fab leukocyte CD11b expression, especially on neutrophils, diminished and remained low for some time (see page 103, column 2)

Mikelson et al. disclose that the 7E3 antibody, including chimeric 7E3, bound Mac-1 and block Mac-1-dependent adhesive properties (see page 104, columns 1-2, overlapping paragraph).

It is noted that elected invention encompass methods of reducing stenosis or restenosis with antibodies that are immunoreactive with Mac-1 and which block the interaction of the integrin or inhibit the expression of the integrin.

Appellant argues that Deitch et al. (Arterioscler. Thromb. Vasc. Biol. 18: 1730-1737, 1998; Exhibit) is supportive of Mikelson with respect to the response to angioplasty and intra-arterial stenting in atherosclerotic nonhuman primates.

Deitch et al. indicate that the data suggests that restenosis may not have been reduced in EPIC, the lack of angiography data from that trials leaves this question unanswered (see page 1735, column 2, paragraph 2).

Deitch et al. disclose that differences in animal species, method of arterial injury, a lack of preexisting atherosclerosis, and the varied anti- β 3 antagonists used in each study preclude direct comparison to the results presented (see page 1736, column 1, lines 18- 22).

Deitch et al. indicate the limitations of the model studied, wherein the lumen narrowing measured in the current study is not truly restenosis but rather loss of the initial gain after angioplasty in an atherosclerotic artery (see page 1736, column 1, paragraph 1, Limitations of the Model).

Appellant further argues that The Eraser Investigators (Circulation 100: 799-806, 1999; Exhibit) show that the Abciximab antibody does not inhibit restenosis.

The EPIC Investigators also state that other factors may influence the interpretations of this study (see page 805, column 2, paragraph 1). First, the results should not necessarily be extrapolated to balloon angioplasty because the mechanisms of restenosis differ. Second, they could not exclude a benefit of larger and possibly longer infusion doses of abciximab or a more powerful or longer-lasting α v β 3 receptor inhibitor. Finally, the important reduction in periprocedural myocardial infarction with abciximab noted in the EPIC, EPILOG and EPISTENT studies with which the data is consistent must be considered.

In the Introduction (page 799, columns 1-2, overlapping paragraph); this reference does acknowledge that abciximab inhibits both integrins (α III β 3 and α v β 3) and has been shown to decrease the incidence of target lesion revascularization after angioplasty. Abciximab also cross-reacts with the leukocyte integrins Mac-1 and intracellular adhesion molecule-1, which mediate inflammation after arterial injury and may be involved in restenosis.

Simon et al. (Circulation 92. 8 Suppl: I-110, Abstract 0519 (1995) clearly teach that the 7E3 antibody is used to inhibit ischemic complications of coronary angioplasty and clinical restenosis and that this 7E3 antibody cross-reacts with Mac-1 (see Abstract).

Coller et al. teach the use of the 7E3 antibody to treat a number of thrombotic conditions (see entire document, including Utility of Platelet-Specific Chimeric immunoglobulin in columns 5-7) in order to prevent or reduce reocclusion following thrombolysis (see column 2, paragraph 1). Example 4 provides evidence that chimeric 7E3 antibody prevent thrombotic complications of coronary angioplasty (see columns 14-26). Example 5 provides evidence that chimeric 7E3 antibody successfully treats abrupt closure of coronary angioplasty by achieved stable reperfusion of acutely occluded coronary arteries (columns 26-29).

Therefore, the prior art clearly teaches the inhibition of stenosis and/or restenosis of a blood vessel following injury to a vascular tissue with the 7E3 antibody, an antibody that cross-reacts with Mac-1.

As pointed out above; Topol et al. (JAMA 278: 479-484, 1997; Exhibit) states that a large number of pharmacological agents have failed to reduce restenosis or improve long-term clinical outcomes and that only the large-scale trial that reported an effect was using abciximab (see page 479, right hand column).

Again, it is noted that the referenced abciximab is a monoclonal antibody fragment against $\alpha IIb\beta 3$, which cross-reacts with Mac-1 and is derived from the 7E3 antibody of the prior art rejections.

This reference clearly supports the rejections under 35 U.S.C. 112, first paragraph, as well as under 35 U.S.C. 102 and 103 of record and reiterated herein.

Also as pointed out previously and in contrast to applicant's assertions; Simon et al. (Arterioscler. Thromb. Vasc. Biol. 17: 528-535, 1997) and Genetta et al. (Annals of Pharmacology 30: 251 -257, 1996) both acknowledged that 7E3 reduced clinical restenosis (see Abstracts).

Appellant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations of inhibiting or reducing stenosis or restenosis of a blood vessel following injury to vascular tissue would be inherent properties of the referenced methods using 7E3 antibodies.

While there are issues associated with the precise mechanism of action associated with the clinical effects of 7E3 and that the interrelationship between stents, platelets and neointimal proliferation may vary between different species and different procedures; It is clear that at the time the invention was made and acknowledged still is that the 7E3 antibody including the chimeric 7E3 Fab inhibited stenosis and restenosis, at least in certain circumstances (e.g. balloon angioplasty).

Appellant's arguments are not found persuasive.

Rejection Under 35 U.S.C. § 103

Appellant's arguments have been fully considered but are not found persuasive essentially for the reasons of record.

Claims 1-6, 8, 10-12 stand rejected under 35 U.S.C. § 103 as being unpatentable over Ricevuti et al. (Atherosclerosis, 1991) AND/OR Albelda et al. (FASEB J., 1994) AND/OR Coller et al. (U.S. Patent No. 5,770,198) AND/OR Simon et al. (Circulation, 1995) in view of art known use of administering pharmaceutical reagents in various composition forms and at various intervention times and in further evidence of Neumann et al. (JACC, 1996) for the reasons of record.

Appellant's arguments and the examiner's rebuttal concerning the teachings of Simon et al. And Coller et al. are addressed above in the rejection under 35 U.S.C. § 102

Simon et al. (Circulation 92, 8 Suppl: I-110, Abstract 0519 (1995) clearly teaches that the 7E3 antibody is used to inhibit ischemic complications of coronary angioplasty and clinical restenosis and that this 7E3 antibody cross-reacts with Mac-1 (see Abstract).

Coller et al. clearly teaches the use of the 7E3 antibody to treat a number of thrombotic conditions (see entire document, including Utility of Platelet-Specific Chimeric immunoglobulin in columns 5-7) in order to prevent or reduce reocclusion following thrombolysis (see column 2, paragraph 1). Example 4 provides evidence that chimeric 7E3 antibody prevent thrombotic complications of coronary angioplasty (see columns 14-26). Example 5 provides evidence that chimeric 7E3 antibody successfully treats abrupt closure of coronary angioplasty by achieved stable reperfusion of acutely occluded coronary arteries (columns 26-29).

Therefore, the prior art clearly teaches the inhibition of stenosis and/or restenosis of a blood vessel following injury to a vascular tissue with the 7E3 antibody, an antibody that cross-reacts with Mac-1

Appellant's arguments in conjunction with certain legal decisions have been fully considered but are not found convincing essentially for the reasons of record and addressed herein.

Appellant argues that Ricevuti al. relates to ischemia and reperfusion, not restenosis

Appellant argues Albelda does not mention restenosis

Appellant argues that Neumann et al. indicates generally that were was neutrophil and platelet activation at the injured artery.

Appellant asserts that an antibody that may be cross-reactive with Mac-1 in vitro but is not cross-reactive in vivo. Appellant provides no objective evidence for this assertion.

Appellant argues that results obtained relative to ischemia and reperfusion are not predictive of results obtained in the treatment of restenosis; that is, the mechanism are different, the treatments are different and the outcomes are different.

Appellant's arguments concerning the differences between reperfusion and restenosis are acknowledged. Also, see the Summary of the Invention above.

The arguments of applicant's representative cannot take the place of evidence in the record. Appellant's reliance on unexpected results do not overcome clear and convincing evidence of obviousness

In contrast to appellant's assertions, the combination of the prior art did provide the ordinary artisan with motivation and an expectation of success that the use of anti-Mac-1 specific antibodies would inhibit stenosis and restenosis associated with vascular intervention given that a property of the 7E3 antibody was to bind and inhibit via the Mac-1 specificity (Coller et al. and Simon et al.); that the Mac-1 specificity was an important target in treating complications associated with vascular intervention (Neumann et al.); that inhibiting PMNs via anti-CD11b/CD18 antibodies inhibited ischemia-reperfusion injury (Ricevuti et al.); that the use of adhesion molecule-specific including blockade of the CD11/CD18 complex had been shown to inhibit neutrophil influx in almost every system to date including the heart and ischemia reperfusion (see Albelda).

As pointed out above; a large number of pharmacological agents have failed to reduce restenosis or improve long-term clinical outcomes and that only the large-scale trial that reported an effect was using the 7E3 antibody or the chimeric 7E3 Fab (abciximab). Again, it is noted that the prior art rejection is based upon this very 7E3 antibody, which binds $\alpha\text{IIb}\beta\text{3}$ and cross-reacts with Mac-1.

The claims encompass inhibiting or reducing stenosis in addition to restenosis.

While there are issues associated with the precise mechanism of action associated with the clinical effects of 7E3 and that the interrelationship between stents, platelets and neointimal proliferation may vary between different species and different procedures; It is clear that at the time the invention was made and acknowledged still is that there was an expectation of success that the 7E3 antibody including the chimeric 7E3 Fab inhibited stenosis and restenosis, at least in certain circumstances (e.g. balloon angioplasty).


Appellant's arguments are not found persuasive for the reasons of record.


(12) For the above reasons, it is believed that the rejections should be sustained.

Respectively submitted,



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